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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,772	02/25/2002	Peter Droge	DEBE:008US	4391

7590 04/19/2005

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,772	DROGE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,32-39,41,43-51 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-30, 32-39, 41, 43-51 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/26/04 has been entered.

Amended claims 29-30, 32-39, 41, 43-51 and 58 are pending in the present application, and they are examined on the merits herein with the elected invention drawn to a method of sequence specific recombination of DNA in a eukaryotic cell in a cell culture or *in vitro* or *ex vivo*.

Response to Amendment

The rejection under 35 U.S.C. 102(e) as being anticipated by Crouzet et al. (US Patent 6,143,530) is withdrawn in light of Applicants' amendment.

The rejection under 35 U.S.C. 102(b) as being anticipated by Hartley et al. (US 5,888,732) is withdrawn in light of Applicants' amendment.

The rejection under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view Hartley et al. (US 5,888,732) is withdrawn in light of Applicants' amendment.

The rejection under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Capecchi et al. (US 5,464,764) is withdrawn in light of Applicants' amendment.

Claim Objections

Claims 34-35 are objected to because of the phrase "further comprising, in step (c), providing to said cell a Xis factor. The labeling step (c) is not in a logical order to the previous steps recited in claim 29 which claims 34-35 are dependent on. This is because the step of further providing to said cell a modified bacteriophage lambda integrase Int would be considered to be step (c), because the recited step (b) simply involves the introduction of a second DNA segment into a eukaryotic cell. Appropriate correction is required.

Claim 29 is objected because it encompasses a non-elected embodiment, specifically a method of sequence specific recombination of DNA in a eukaryotic cell in a vertebrate organism (Invention of Group II, see restriction requirement). Appropriate correction is required.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 29-30, 32-39, 43-51 and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection.***

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's elected invention is drawn to a method of sequence specific recombination of DNA in a eukaryotic cell *in vitro* or *ex vivo*, the method comprises the steps of providing a eukaryotic cell comprising a first DNA segment with a second DNA segment, wherein the DNA segments have the limitation recited in claim 29 and wherein the cell is further provided with any modified bacteriophage λ integrase which induces sequence specific recombination through *att*B and *att*P or *att*R and *att*L sequences in the first and second DNA segments.

However, apart from disclosing two mutant bacteriophage λ integrases, Int-h (E174K) and the double mutant Int-h/218 (E174K/E218K), the instant specification fails to describe structural characteristics of any other modified bacteriophage λ integrases

having functional properties similar to Int-h and/or Int-h/218 in inducing sequence specific recombination through *att*B and *att*P or *att*R and *att*L sequences. Nor does the instant specification describe any structural characteristic for any modified Int factor to be utilized in the method of amended claim 49 other than the aforementioned bacteriophage λ integrase mutants. The instant specification further fails to provide a representative number of species for a broad genus of a modified bacteriophage λ integrase or a modified Int factor.

At about the effective filing date of the present application (8/29/00), the prior art does not describe any other modified bacteriophage λ integrases or any modified Int factor apart from the Int-h and Int-h/218 mutants as evidenced by the teachings of Hartley et al. (US 5,888,732); Crouzet et al. (US Patent 6,143,530), and Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS).

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a broad genus of modified bacteriophage λ integrases or a modified Int factor to be utilized in the methods as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 49, it is unclear what is encompassed by the phrase "performing a second sequence specific recombination of DNA by modified Int factor and a Xis factor after the steps (a)-(b)". Clarification is requested because steps (a)-(b) in the amended claim 29 simply involve the introduction of a second DNA segment into a eukaryotic cell comprising a first DNA segment, and thus there is no apparent recombination event occurring. Then how a second sequence specific recombination of DNA is performed? The metes and bounds of the claims are not clearly determined.

Additionally, it is unclear what is encompassed by the term "modified Int factor". Do Applicants refer or mean a modified bacteriophage lambda Integrase or a modified Integrase? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Amended claims 29-30, 32-33, 41, 44-48 and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by Lorbach et al. (J. Mol. Biol. 296:1175-1181, 2000, IDS).

Lorbach et al disclose a method in which pGFPattB/attP or pGFPattL/attR was co-introduced either with pPGKInt-h or pKEXInt-h to human HeLa or BL60 cells, and demonstrate that phage λ Int-h is proficient at performing integrative and excisive recombination on episomal DNA substrates in these two different cell lines (page 1176, col. 2, first two paragraphs). Lorbach et al further demonstrated that mutant Int proteins (Int-h and Int-h/218) are proficient to perform intramolecular, integrative recombination between attB/attP at genomic target sites in two different human cell lines, but little exicisive recombination between attL and attR on a genomic substrate was detected using these mutant Int proteins (page 1178, col. 2, first two full paragraphs). Lorbach et al further teach that the λ Int recombination system can be further refined through the additional use of accessory proteins such as XIS (page 1179, col. 2, bottom of first full paragraph; page 1180, col. 2, first full paragraph). It is further noted that the results taught by Lorbach et al are the same results presented by the present application.

Accordingly, Lorbach et al anticipate the instant claims.

Response to Arguments

Applicants' argument with respect to the above rejection in the Amendment filed on 11/26/04 (pages 6-7) has been fully considered but it is respectfully not found persuasive.

Applicants argue mainly that Applicants will be submitting a certified copy of the priority document to perfect the priority claim.

It is noted Applicants cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 29, 32-35, 41, 44-45 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. (US 5,888,732) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS). ***This is a new ground of rejection necessitated by Applicants' amendment.***

Hartley et al disclose a method of making chimeric DNA comprising the steps: (a) combining *in vitro* or *in vivo*, (b) an Insert Donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site, wherein the first and second recombination sites do not recombine with each other; (c) a Vector Donor DNA molecule containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination site do not recombine with each other; and (d) one or more site specific recombination proteins capable of recombining the first and third recombination sites and/or the second and fourth recombination sites (see Summary of the Invention, and Figures 1-2A-F). Figure 1 depicts a general method of Hartley et al., involving two recombination events with two different recombinases that recognize different recombination sites. Hartley et al also teach that the exchange of DNA segments can be achieved by the use of various recombination proteins described in the art (col. 13, line 57 continues to line 24 of col. 16). Hartley et al further teach that examples of recognition sequences to be utilized include attB, attP, attL, and attR sequences which are recognized by the recombinase enzyme λ Integrase as well the λ Integrase (col. 8, lines 43-63). The disclosed attB sequence of SEQ ID NO:32 comprises the sequence that is identical to SEQ ID NO:1 of the present application, and therefore the corresponding attP recombination sequence must have the same SEQ ID NO: 2 of the present application, or at least a derivative thereof. Furthermore, the attL and attR recombination sequences that are catalyzed by the bacterial λ Integrase as taught by Hartley et al. must have the same SEQ ID NO:3 and SEQ ID NO:4, respectively, or a derivative thereof. The desired DNA segment

includes a selectable marker (DNA segments that encode beta-galactosidase, GFP or cell surface proteins), an antisense oligonucleotide or a toxic gene (col. 9, lines 5-36), and that host cells include *E.coli* cell lines as well as eukaryotic cells (col. 13, lines 35-55). Hartley et al. also teach the use of integrase in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL to form attP and attB in their method (col. 15, lines 1-4), as well as the use of IHF proteins for the recombination at attB and attP sites (col. 14, lines 26-30). Hartley et al. also teach engineered att recombination sites having one or multiple mutations to enhance specificity or efficiency of the recombination reaction, and that a tripartite protein fusion could be accomplished with parental plasmids containing recombination sites attR1 and attR2; attL1 and attL3; and attR3 and attL2 (col. 16, lines 26-61; col. 17, line 47 continues to line 46 of col. 18).

Hartley et al do not specifically teach the use of any modified λ Integrase, specifically Int-h or Int h/218.

However, at the effective filing date of the present application Christ & Droge already teach the mutant λ Integrases, Int-h and Int-h/218, that are capable of catalyzing λ site-specific recombination *in vivo* in the absence of host co-factors IHF, Fis and Xis (see abstract). Christ & Droge further teaches that the potential of these mutants to perform recombination in the absence of accessory factors is due to their enhanced affinity for core sites, and that Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase (page 827, left column, second full paragraph; page 828, left column, top of last paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Hartley et al. by also utilizing the mutant λ Integrases, Int-h and Int-h/218, of Christ & Droge in their method of making a chimeric DNA due to the advantages offered by these mutant integrases. Please also note that this modification does not exclude the use of wild-type λ Integrases altogether in the method of Hartley et al, depending on the pair of target recombination sites and the desired recombination efficiency.

An ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Christ & Droge, the mutant integrases are capable of catalyzing λ site-specific recombination *in vivo* in the absence of host co-factors IHF, Fis and Xis, and more particularly Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hartley et al., Christ & Droge, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect in part to the above rejection in the Amendment filed on 11/26/04 (page 8) have been fully considered but they are respectfully not found persuasive.

Applicants argue mainly that Hartley et al. do not provide any teachings regarding to the preparation and/or use of mutant/modified integrase proteins displaying differing characteristics concerning co-operativity with its co-factors. Based on the statements in Hartley et al., the artisan in the field would not even be aware of the advantages offered by the mutant integrases as described by Christ & Droge. Therefore, a skilled artisan would not have combined the teachings of Christ & Droge with the teachings of Hartley et al. in order to arrive at the present invention.

Please note that Hartley et al clearly teach that the exchange of DNA segments can be achieved by the use of various recombination proteins described in the art, including a bacteriophage lambda Int system (col. 13, line 57 continues to line 24 of col. 16). The mutant integrases described by Christ & Droge are recombination proteins described in the prior art. As already noted above, an ordinary skilled artisan would be motivated to modify the method taught by Hartley et al. by utilizing the mutant λ Integrases, Int-h and Int-h/218 of Christ & Droge due to the advantages offered by the mutant integrases, specifically because the mutants are capable of catalyzing λ site-specific recombination *in vivo* in the absence of host co-factors IHF, Fis and Xis, and more particularly Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

Accordingly, amended claims 29, 32-33, 41, 44-45 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. in view of Christ & Droge for the reasons discussed above.

Amended claims 29-30, 32-33, 41, 44-48 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS). ***This is a new ground of rejection necessitated by Applicant's amendment.***

Crouzet et al teach a method for producing therapeutic DNA molecules by excision from a plasmid or from a chromosome by site-specific recombination, wherein the site-specific recombination is carried out in a host cell or *in vitro*, and wherein the site-specific recombination is carried out by means of various systems which lead to site-specific recombination between sequences (col. 3, line 27 continues to line 20 of col. 4; Figures 1-2). Specifically, Crouzet et al disclose that the gene or genes of interest flanked by the two sequences permitting site-specific recombination, positioned in the direct orientation in a vector, a phage or a virus, and the specific recombination sequences and recombinases used can belong to different structural classes, including the integrase family of bacteriophage λ and the attP and attB sequences catalyzed by the phage lambda integrase (col. 4, lines 21-52; col. 5, lines 32-41). The disclosed attB sequence is identical to SEQ ID NO:1 of the present application (see SEQ ID NO:6), and therefore the corresponding attP recombination sequence must have the same SEQ ID NO: 2 of the present application, or at least a derivative thereof. Additionally,

Crouzet et al. teach that their genetic constructs can be used for the construct of cell hosts having disclosed elements integrated in their genomes (col. 4, lines 4-9, and Figure 1). Crouzet et al further teach that the recombinase used can be under the control of a promoter or a system of inducible promoters, and it can be carried by a plasmid, a phage or even in the non-therapeutic region of the recombinant DNAs (col. 7, line 45 continues to line 39 of col. 8), and that any type of host cell can be used including eukaryotic cells such as yeasts, animal cells, plant cells, mammalian cells such as CHO, COS and mouse NIH3T3 (col. 9, lines 48-60). Crouzet et al also disclose that their genetic constructs comprise one or more genes of interest such as the genes coding for enzymes, hormones, growth factors, apolipoproteins, tumor suppressor genes, suicide gnes, natural or artifical immunoglobulin or an antigenic peptide (col. 13, lines 14-50).

Crouzet et al do not specifically teach the use of any modified λ Integrase, specifically Int-h or Int h/218 in their method of producing therapeutic DNA molecules, even though they teach that any specific recombination sequences and appropriate recombinases can be used, including those belonging to the bacteriophage λ system.

However, at the effective filing date of the present application Christ & Droge already teach the mutant λ Integrases, Int-h and Int-h/218, that are capable of catalyzing λ site-specific recombination *in vivo* in the absence of host co-factors IHF, Fis and Xis (see abstract). Christ & Droge further teaches that the potential of these mutants to perform recombination in the absence of accessory factors is due to their enhanced affinity for core sites, and that Int-h is known to recombine pairs of att sites

which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase (page 827, left column, second full paragraph; page 828, left column, top of last paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Crouzet et al by utilizing specifically the mutant λ Integrases, Int-h and Int-h/218, of Christ & Droge in their method of producing therapeutic DNA molecules due to the advantages offered by the mutant integrases.

An ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Christ & Droge, the mutant integrases are capable of catalyzing λ site-specific recombination *in vivo* in the absence of host co-factors IHF, Fis and Xis, and more particularly Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Amended claims 29 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) as applied to claims 29-30, 32-33, 41, 44-48 and 58

above, and further in view of Capecchi et al. (US 5,464,764). ***This is a new ground of rejection necessitated by Applicant's amendment.***

The teachings of Crouzet et al. and Christ & Droge have been discussed above. However, neither Crouzet et al nor Christ & Droge teach that the first and/or the second DNA segment further comprising a sequence effecting integration of said first and/or second DNA segment into the genome of a cell by homologous recombination, even though Crouzet et al teach specifically that the genetic constructs can be used for the construct of cell hosts having disclosed elements integrated in their genomes (col. 4, lines 4-9, and Figure 1).

However, at the effective filing date of the present application Capecchi et al. already describe a well-known method and a positive-negative selector vectors comprising sequences to be introduced in the genome of a target cell by the homologous recombination approach (see abstract and Figure 1).

It would have been obvious for an ordinary skilled artisan to further modify the modified method of Crouzet et al and Christ & Droge by introducing the genetic construct in the form of a positive-negative selector vector described by Capecchi et al. into a target host cell capable of homologous recombination to incorporate their genetic construct in the genome of the host cell as specifically taught by Crouzet et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the approach taught by Capecchi et al. overcomes many problems associated with random integration, and that the gene of interest can be introduced into any predetermined region of the genome of a target host cell.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge and Capecchi et al, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Quang Nguyen, Ph.D.

QUANG NGUYEN, PH.D
PATENT EXAMINER